REMARKS

The Final Office Action mailed October 18, 2002 has been received and reviewed. Claims 1-11, 14-19 and 21-23 are pending in the application. All claims stand finally rejected. Applicants propose to amend claims 6, 11 and 15-18, add new claim 24 and have cancelled claim 19 as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11 and 15-19 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 19 has been cancelled rendering the rejection thereof moot. Partially in view of the amendments to claims 11 and 15-18 and the addition of new claim 24, applicants respectfully traverse the rejections.

Claim 11 was thought to be indefinite for use of the word "interfere." Although applicants do not agree that claim 11 is indefinite, for the sake of expedited prosecution, applicants propose to amend claim 11 in accordance with the examiner's suggestion and replace the phrase "interferes with" with the term "inhibits." Reconsideration and withdrawal of the indefinite rejection of claim 11 are thus requested.

Claims 15-18 were deemed indefinite since it was thought that the steps recited by the methods do not necessarily achieve the goal set forth in the preamble. While the applicants do not agree that the claims are indefinite, as proposed to be amended claim 15 recites in part a "method of screening for an orphan receptor and its unknown ligands." Claim 15 further recites "providing a eukaryotic cell comprising: a first recombinant gene encoding a chimeric receptor; a library of recombinant genes encoding at least one compound, the expression of which creates an autocrinic loop."

As proposed to be amended, claim 15 should be considered definite since the unknown ligand includes the at least one compound, even if the compound is known, according to the definition of "unknown ligand" in the specification. As defined in the specification an "unknown ligand" refers to "every compound that can interact with or bind to a receptor [] for which this

interaction or binding has not yet been demonstrated." (Specification as filed, paragraph **[0035]**). The screening method of claim 15 is accomplished by providing a eukaryotic cell including a chimeric receptor made up of the orphan receptor and a library of recombinant genes which encode the at least one compound, the expression of which creates an autocrinic loop to activate the reporter system. As defined in the specification, "orphan receptor" includes "every receptor, preferably a multimerizing receptor or protein with known receptor components of which no known ligand is known, that is interacting or binding to this receptor, and as a consequence, initiating or inhibiting the signaling pathway." (*Id.* at paragraph **[0033]**). Thus, as proposed to be amended, claim 15 is directed to screening for unknown ligands that bind the orphan receptor and should be considered definite.

As proposed to be amended, claim 18 depends from claim 15 and recites in part "wherein said unknown ligands are produced by the autocrinic loop" wherein the phrase "or anti-autocrinic loop" has been removed. Accordingly, claim 18 should be considered definite.

New claim 24 is proposed to be added. New claim 24 is directed to a method of screening for antagonists interfering with ligand-receptor binding and provides antecedent basis for dependent claims 16 and 17.

Claim 16 was thought to be indefinite for reciting the phrase "series of compounds." For clarification, applicants propose to amend claim 16 to depend from new claim 24 which includes the step of "reacting a series of compounds with said eukaryotic cell." Accordingly, new claim 24 provides antecedent basis for claim 16 and should render claim 16 definite.

As proposed to be amended, claim 17 depends from claim 16 and recites in part "wherein said antagonists create the autocrinic loop." Accordingly, claim 17 should be considered definite.

In view of the amendments and remarks presented herein, reconsideration and withdrawal of the indefinite rejections of claims 11 and 15-18 are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 14 and 21-23

Claims 1-6, 14 and 21-23 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. Applicants respectfully traverse the rejections as hereinafter set forth.

A *prima facie* case of obviousness has not been established with regard to independent claim 1 since no suggestion or motivation exists in the cited references to combine the references. No suggestion or motivation exists in Trueheart et al. to use a chimeric receptor. Rather, Trueheart et al. is limited to the expression of polypeptides from a library to identify polypeptides that agonize or antagonize receptor bioactivity. (*See*, Trueheart et al., page 3). Muthukumaran et al. is limited to the study of chimeric receptor complexes, and does not suggest or motivate the use of a eukaryotic cell comprising the chimeric receptor combined with a screening method using a library of polypeptides and a reporter system. (*See*, Muthukumaran et al., page 4993). In view of these limitations, no suggest or motivation exists in the cited references to combine the reference teachings.

Further, a *prima facie* case of obviousness cannot be established since one of skill in the art would not have a reasonable expectation of success in combining the teachings of Trueheart et al. with Muthukumaran et al. As stated in the Office Action "the chimeric receptor of Muthukumaran et al. might not be functional in yeast cells" indicating that one of skill in the art would not expect the chimeric receptor of Muthukumaran et al. to be functional in the yeast cells of Trueheart et al. (Final Office Action, mailed October 18, 2002, page 4). In the alternative, the Office Action states "the autocrinic loops in yeast cells taught by Trueheart et al. would assume to work in CHO-B7 and CHO-16-9 cells that express chimeric receptors, as taught by Muthukumaran et al., absence evidence to the contrary. One skilled in the art would be able to combine the autocrinic loops taught by Trueheart et al. with the chimeric receptors in CHO-B7 and CHO-16-9 cells taught by Muthukumaran et al. with a reasonable expectation of success." (*Id.* at page 4).

Applicants respectfully disagree with the presumption of a reasonable expectation of success as suggested by the Office. It is unlikely that one of skill in the art would reasonably

expect the autocrinic loops of the yeast cells of Trueheart et al. to be functional in the CHO-B7 and CHO-16-9 cells of Muthukumaran et al. since CHO-B7 and CHO-16-9 cells produce a background (*i.e.*, the hundreds of GPCRs in the CHO cells may produce false positives or constitutively produce signal) that may make screening in the mammalian cells nearly impossible. For instance, as known in the art, a review article indicates that mammalian cells include several hundreds of G-protein coupled receptors (GPCRs) while only two GPCRs have been identified in yeast. (*See, e.g.,* Versele et al., *Sex and sugar in yeast: two distinct GPCR systems*, EMBO *reports*, vol. 2, no. 7, 574-579 (2001)) (attached hereto).

Further, it is known in the art that "one factor which can complicate the use of heterologous expression systems for ligand fishing involves the presence of endogenous receptors in mammalian cell lines and in particular, clonal variation in the pattern of endogenous receptor expression in cells derived from the same parental cell line." (Wilson et al., *Orphan G-protein-coupled receptors: the next generation of drug targets?*, British Journal of Pharmacology, vol. 125, 1387-1392, at p. 1389 (1998)) (attached hereto). Since yeast cells have a small number of GPCRs, "the ability to genetically delete endogenous GPCRs from yeast to generate a 'null' background is one of the major advantages in using yeast model systems for orphan receptor screening." (*Id.* at 1390). Thus, no one of skill in the art would reasonably expect the autocrinic loops of the yeast cells of Trueheart et al. to work in the mammalian cells of Muthukumaran et al.

An additional reason why one skilled in the art would not expect the autocrinic loops of Trueheart et al. to function in the mammalian cells of Muthukumaran et al. is that the responsive CHO cells of Muthukumaran et al. are not normal mammalian cells. The "normal" parental cell line CHO-BH7 of Muthukumaran et al. was shown to be not responsive. (*See*, Muthukumaran et al., page 2994). The CHO-B7 cells of Muthukumaran et al. transfected with IFNγR2 or γR2/EPOR cDNA showed no response to Hu-INFγ since the "normal" CHO-BH7 cells lack the ligand-binding receptor subunit Hu-IFN-γR1. (*See, Id.*). Responsiveness in Muthukumaran et al. was obtained in the specially designed 16-9 hamster x human somatic hybrid cell line which contains a translocation of the long arm of human chromosome 6 and the human HLA-B7 gene. (*Id.* at 4993).

Thus, one of skill in the art would not expect the mammalian cells of Muthukumaran et al. to be a suitable host for the autocrinic loops of Trueheart et al. Without a reasonable expectation of success to combine the cited references, a *prima facie* case of obviousness cannot be established.

Regarding dependent claims 2-6, 14 and 21-23, they are nonobvious at the very least as depending from nonobvious independent claim 1. (*See*, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

Accordingly, applicants request reconsideration and withdrawal of the obviousness rejections of independent claim 1, and claims 2-6, 14 and 21-23 depending therefrom.

Claims 7-11

Claims 7, 8 and 10 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied above, and further in view of Pellegrini et al.; claim 9 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied above, and further in view of Mizushima et al.; and claim 11 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. Applicants respectfully traverse the rejections as herein set forth.

Claims 7-11 are nonobvious, at the very least, as directly or indirectly depending from nonobvious independent claim 1. (*See*, *In re Fine*, *supra*).

With further regard to claims 7, 8 and 10, they should be considered nonobvious since no suggestion or motivation exists to combine the reference teachings. Pellegrini et al. is limited to a genetic selection method for isolating regulatory mutations in a signaling pathway for alpha interferon and does not suggest or motivate the use of a chimeric receptor, an autocrinic loop or a reporter system. (*See*, Pellegrini et al., Abstract). Further, neither Muthukumaran et al. nor Trueheart et al. suggests or motivates the use of *E. coli* xanthine-guanine phosphoribosyl transferase, a 6-16 reporter or a 2fTGH cell as required to establish a *prima facie* case of obviousness.

Claim 9 should further be considered nonobvious since Mizushima et al. is limited to the construction of an expression vector using the EF-1α promoter and does not suggest or motivate the use of the EF-1α promoter in combination with the chimeric receptor, the autocrinic or anti-autocrinic loop or the reporter system of claim 1. (*See*, Mizushima et al., page 5322). Also, the Office has not indicated where Muthukumaran et al. or Trueheart et al. suggest or motivate the use of the EF-1α promoter.

Claims 15-19

Claims 15-18 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. and claim 19 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Trueheart et al. in view of Muthukumaran et al. as applied to claims 11 and 15-18 above, and further in view of Watowich et al. Claim 19 has been cancelled rendering the rejection thereof moot. Applicants respectfully traverse the rejections of claims 15-18 as hereinafter set forth.

Independent claim 15 is nonobvious since a *prima facie* case of obviousness has not been established. As previously set forth herein, no suggestion or motivation exists in Trueheart et al. or Muthukumaran et al. to combine the reference teachings. Further, one of skill in the art would not expect the mammalian cells of Muthukumaran et al. to be a suitable host for the autocrinic loops of Trueheart et al. and without a reasonable expectation of success, a *prima facie* case of obviousness cannot be established.

New claim 24 should be considered nonobvious since a *prima facie* case of obviousness cannot be established. Since no suggestion or motivation exists to combine Trueheart et al. with Muthukumaran et al. and one of skill in the art would not have a reasonable expectation of success in combining the references, new claim 24 is nonobvious.

Claims 16-18 are nonobvious, at the very least, as depending from nonobvious independent claim 15 or 24. (*Id.*).

ENTRY OF AMENDMENTS

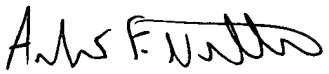
The proposed amendments to claims 6, 11 and 15-18 and the addition of new claim 24 should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. The amendments to claims 11 and 15-18 should not raise new issues or require a further search since the amendments comply with requirements as to form. New claim 24 should be entered because it is supported by the as-filed application and should not require a further search. For instance, the limitations of new claim 24 were present in claim 15 as originally filed. The amendments should also place the application in condition for allowance. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after

consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



Andrew F. Nilles
Registration No. 47,825
Attorney for Applicants
TRASKBRITT, PC
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

Date: December 18, 2002
AFN/afn
Document in ProLaw

Enclosures: Versele et al., *Sex and sugar in yeast: two distinct GPCR systems*, EMBO *reports*, vol. 2, no. 7, 574-579 (2001)
Wilson et al., *Orphan G-protein-coupled receptors: the next generation of drug targets?*, British Journal of Pharmacology, vol. 125, 1387-1392 (1998)

MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

6. (Amended) The eukaryotic cell of claim 1 wherein a cytoplasmic part of the chimeric receptor is a cytoplasmic part [of one] of at least one interferon receptor subunit.

11. (Thrice Amended) A method of screening a compound that [interferes with] inhibits the binding of a ligand with the extracellular part of a chimeric receptor and/or with the signaling pathway of the cytoplasmic part of a chimeric receptor, the method comprising:
providing the eukaryotic cell of claim 1;
contacting said eukaryotic cell with said compound; and
selecting cells in which the cell's reporter system is inactivated.

15. (Twice Amended) A method of screening for an orphan [receptors] receptor and its unknown ligands comprising:
providing a eukaryotic cell comprising:
a first recombinant gene encoding a chimeric receptor;
a [second recombinant gene] library of recombinant genes encoding [a] at least one compound, the expression of which creates an autocrinic loop;
a reporter system that is activated upon the creation of said autocrinic loop; and
selecting cells in which the cell's reporter system is activated.

16. (Amended) The method according to claim [15] 24 wherein said series of compounds comprise genes encoding [candidate inhibitors] said antagonists.

17. (Amended) The method according to claim 16 wherein said [inhibitors] antagonists create [an] the autocrinic [or anti-autocrinic] loop.

18. (Amended) The method according to claim 15 wherein said unknown ligands are produced by [an] the autocrinic [or anti-autocrinic] loop.